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WIGGIN & DANA, LLP
DOCKET COORDINATOR
ONE CENTURY TOWER
P.O. BOX 1832
NEW HAVEN, CT 06508-1832

EXAMINER
EPPERSON, JON D

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
File Copy	09/830,080	UHLEN ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *2-7, 8-13 (in part), 15-16 and 20-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-14 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11,13* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *16* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on June 30, 2003 (Paper No. 15).

Priority Claims

2. The priority filing date of October 21, 1998 for 9823071.7 (Great Britain) is acknowledged.

Status of the Claims

3. Claims 1-26 are pending in the present application.

4. Applicant's response to the Restriction and/or Election of Species requirements in Paper No. 15 is acknowledged (Applicant elected Group I, claims 1, 8 (in part), 9-13 (in part), 14 and 17-19, see also interview summary) and claims 2-7, 8 (in part), 9-13 (in part), 15-16 and 20-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., ***Response to Restriction and/or Election of Species***).

5. Therefore, claims 1, 8 (in part), 9-13 (in part), 14 and 17-19 are examined on the merits in this action.

Response to Restriction and/or Election of Species

6. Applicant's election of Group I (claims 1, 8 (in part), 9-13 (in part), 14 and 17-19) in Paper No. 15 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement (with the exception of claim 16, see below), the election has been treated as an election without traverse (MPEP § 818.03(a)).

7. With regard to claim 16, Applicants traversed the election requirement on the grounds that "dependent claim 16 is more properly associated with the claims of Group I (method for affinity separation) rather than Group IV (method of phage display)" because it is dependent on claim 14.

8. These arguments were fully considered but were not found persuasive. The Examiner's position is that the "subject matter" of claim 16 is drawn to a "phage display" and not an "affinity chromatography" method as set forth in the original restriction i.e., Group I does not require a "phage display" (see Paper No. 12, paragraph 5). Therefore, a special technical feature does not link claim 16 with Group I.

9. Applicant's election of species in Paper No. 15 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the

election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

10. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

11. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

12. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Specification

13. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). Here, there is no reference for PCT/GB99/03484 filed 10/21/1999. A reference to a foreign application (i.e., 9823071.7) is not required.

14. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims Rejections - 35 U.S.C. 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

15. Claim 8 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1, 8-14 and 17-19 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claim 1 outlines method steps for the use of "proteinaceous ligands" wherein one or more of the asparagine residues of the proteinaceous ligands has been "modified" presumably to impart some stability in alkaline solution to the ligand. The scope of this claim includes an infinite number of methods for producing an infinite number of structural variants (i.e., asparagine "modified" proteinaceous ligands) wherein no distinguishing structural attributes are provided for these modified proteinaceous ligands (i.e., distinguishing structural attributes that will allow the unrelated proteins to retain their functional properties and chemical stability). The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the modified proteinaceous ligands. Although the specification discloses example of albumin-binding domain asparagine mutants and there are a few other examples known in the literature (e.g., see Specification, examples; see also 35 USC 102(b) rejection below), the specification and claims do not provide ***any*** guidance as to what structural features ***all*** of these proteinaceous ligands share that will allow them to continue to function as a ligand (to an unspecified target) and will also allow them to resist alkaline conditions (see claim 9). Consequently, it is not possible to determine *a priori* which protein/peptide asparagine mutants would be encompassed because there is no common structural attributes or teaching in the specification that can link together ***all*** of these potential

protein/peptide mutants i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* ***all*** the different types of mutant protein/peptides that should be included in this genus from the few examples provide by Applicants.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing examples like albumin-binding domain mutants (see specification, Examples) is insufficient to teach the entire genus. In addition, the art teaches that finding mutants that will retain their inherent binding characteristics and possess the increased stability that is required here cannot be taught (i.e., is inherently unpredictable). For example, Applicants admit "modifications [like the ones presently claimed] may change the function or the potency of a protein or a peptide" and that the "deamidation rate is highly sequence and conformation dependent [this is the reason why the Asn residues are modified i.e., to protect against deamidation]" and thus a person of skill in the art could not predict which Asn residues to modify (see Applicants paper i.e., Gulich, S.; Linhult, M.; Stahl, S.; Hober, S. "Engineering streptococcal protein G for increased alkaline stability" *Protein Engineering* **2002**, *15*, 10, 835-842, especially page 835, paragraph 2). Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus in light of the unpredictable art. Thus, applicant was not in possession of the claimed genus.

17. Claims 1, 8-14 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for albumin-binding domain asparagine mutants, does not reasonably provide enablement for any asparagine "modified" proteinaceous ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are drawn to a broad genus. The scope of this claim includes an infinite number of methods for producing an infinite number of structural variants (i.e., asparagine "modified" proteinaceous ligands) wherein no distinguishing structural attributes are provided for these modified proteinaceous ligands (i.e., distinguishing structural attributes that will allow the unrelated proteins to retain their functional properties and chemical stability). The specification and claims do not place any limit on the number of atoms, the types of

atoms, or the manner in which said atoms might be connected to form the modified proteinaceous ligands. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: Applicants admit that the prior art is inherently unpredictable. For example, Applicants state "modifications [like the ones presently claimed] may change the function or the potency of a protein or a peptide" and that the "deamidation rate is highly sequence and conformation dependent [this is the reason why the Asn residues are modified i.e., to protect against deamidation]" and thus a person of skill in the art could not predict which Asn residues to modify (see Applicants paper i.e., Gulich, S.; Linhult, M.; Stahl, S.; Hober, S. "Engineering streptococcal protein G for increased alkaline stability" *Protein Engineering* **2002**, *15*, 10, 835-842, especially page 835, paragraph 2).

Furthermore, it is well recognized in the art that "modifying" proteins can have a destabilizing and unpredictable effect on the structure and function of the protein i.e., the "modifications" can destroy the stability and also its ability to act as a ligand. For example, destabilizing perturbations in protein–protein interactions can arise from numerous sources as a consequence of a mutation. Some mechanisms involve static interactions at the site of substitution: (a) loss of optimal van der Waals contacts; (b) loss of electrostatic pairings, which provide substantial binding energy compared to solvent; (c) loss of essential electrostatic pairings, which are not net-stabilizing relative to solvent; and (d) loss of buried nonpolar surface area. However, others involve ensemble phenomena, which are not easily recognized or interpreted: (e) a discrete local

conformational change; (f) local unfolding at the interface; (g) increased entropy of unbound states; (h) aggregation; and (i) global unfolding. In particular, changes in interface dynamics (e–g) are very hard to demonstrate or rule out experimentally because of the limitations of available technology. These effects, which relate to the plasticity of protein interfaces, account for much of the current uncertainty in the interpretation of alanine scanning data [i.e., the effects of mutations]. See Delano (Delano, W. L. "Unraveling hot spots in binding interfaces: progress and challenges" Current Opinion in Structural Biology 2002, 12, pages 14-20, especially figure 3).

Therefore, the Examiner contends that the level of predictability in the art is low or absent.

Reference needed ###.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants provide only one example of an albumin-binding domain.

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445

* n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 1, 8-13, 14 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. ***Claim 1*** is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Applicants do not recite ***any*** positive method or process steps and, as a result, it is unclear what method/process steps Applicants are intending to encompass. Therefore, claim 1 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

B. ***Claim 1*** is rejected because the "proteinaceous" ligand in this claim is not defined with any chemical or physical characteristic, but only by functional properties i.e., its ability to act as an "affinity ligand". A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention. A person of skill in the art cannot immediately envision all the possible chemical structures for a peptide with this function. Thus, the metes and bounds of the claimed invention cannot be determined. See *ex parte Pulvari* (POBA 1966) 157 USPQ 169. Therefore, claim 1 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

C. ***Claim 8*** provides for the "use" of a "protein molecule stabilized by modification of one or more of its Asn residues", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Therefore, claim 8 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

D. For **claim 12**, the phrase "the ligand or protein are modified" is vague and indefinite. For example, it is not clear what the "protein" refers to because claim 1 from which claim 12 depends only refers to a "ligand" (albeit a "proteinaceous" ligand). If Applicants intend for the "ligand" and the "protein" to be the same thing then why do Applicants use an "or" i.e., "ligand or protein"? Applicants are requested to clarify and/or correct. Therefore, claim 12 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

E. ***Claim 17*** recites "fragment or derivative thereof" in line 2 and "fragment, domain or derivative thereof" in line 3 and "fragment or domain thereof" in line 4. The terms "fragment" and "derivative" are relative terms, which renders the claim indefinite and/or unclear. The terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore claim 17 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

F. ***Claim 18*** recites "derivative" in line 2. The term "derivative" is a relative term, which renders the claim indefinite and/or unclear. The terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore claim 18 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

G. ***Claim 19*** recites "fragment or derivative thereof" in line 2. The terms "fragment" and "derivative" are relative terms, which renders the claim indefinite and/or unclear. The terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore claim 18 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 1, 8-14 and 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Ahern et al (Ahern, T. J.; Casal, J. I.; Petsko, G. A.; Klibanov, A. M. "Control of oligomeric enzyme thermostability by protein engineering" PNAS **1987**, 84, 675-679).

For ***claim 1***, Ahern et al (see entire document) discloses the use of Asn mutants to increase the stability of yeast triosephosphate isomerase against the pH dependent inactivation of the protein via a deamidation of the asparagine residues (see Ahern et al, abstract; see also page 675, column 1, paragraph 2), which anticipates claim 1. For example, the (Asn-14 → Thr-14 and Asn-78 → Ile-78) mutant triosephosphate isomerase was used in immunoadsorption chromatography (see Ahern et al, abstract; see also page 677, column 1, last paragraph). Here two asparagines have been modified to threonine and isoleucine. The mutant triosephosphate isomerase can be considered an "immobilized proteinaceous ligand" because the mutant is a protein and it is a ligand that becomes immobilized to the chromatography support via immunoadsorption.

For ***claim 8***, Ahern et al discloses the use of the stabilized Asn triosephosphate isomerase mutant in immunoadsorption chromatography (see Ahern et al, page 677, last paragraph, "The wild type and mutant forms of the enzyme were purified ... by immunoadsorption chromatography").

For ***claim 9***, Ahern et al discloses Asn-14 → Thr-14 and Asn-78 → Ile-78 mutations wherein both Thr-14 and Ile-78 are less alkaline sensitive amino acids (see Ahern et al, abstract).

For ***claims 10-11***, Ahern et al discloses two Asn mutations i.e., Asn-14 → Thr-14 and Asn-78 → Ile-78 (see Ahern et al, abstract). Furthermore, mutating more Asn residues would be immediately envisioned by a person of skill in the art because the effects on stability are cumulative and thus a person of skill in the art would immediately envision changing as many Asn residues as are necessary to obtain the requisite degree of stability.

For ***claim 12***, Ahern et al discloses "surface" modifications (e.g., see Ahern et al, page 677, figure 2).

For ***claim 13***, Ahern et al discloses Asp-78 (see Ahern et al, page 678, Table 2).

For ***claim 14***, Ahern et al discloses a library of proteins with Asn mutations e.g., wild type, Thr-78, Ile-78, Thr-14/Ile-78, Asp-78 (see Ahern et al, abstract, see also Table 2 and figures 2-3).

For ***claims 17-19***, Ahern et al discloses triosephosphate isomerase (see abstract) and other proteins like lysozyme, ribonuclease and bacterial α-amylase (see Ahern, page 677, column 1, paragraph 1) that could be used with the disclosed method that would fall within the scope of the "derivatives" claimed by Applicants (see 35 U.S.C. § 112, second paragraph rejection, above).

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.
August 30, 2003

BENNETT CELSA
PRIMARY EXAMINER